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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,979	CAROZZI ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/30/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *12-18,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11,19 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-11, 19 and 22-23) and SEQ ID NO:1 in the reply filed on 30 November 2005 is acknowledged. The traversal is on the ground(s) that DNA and amino acids sequences are related. This is not found persuasive because the searches are made in different databases. A search for a DNA encoding a given protein is made in the nucleic acid databases, while a search for a protein is made in the protein databases. Thus, the searches are not coextensive, and searching both DNA and protein is an undue burden on Office resources.

Applicant also urges that SEQ ID NOs:2 and 4 are fragments of SEQ ID NO:1. This is found persuasive, and the restriction between SEQ ID NOs:1, 2 and 4 is withdrawn. Similarly, the restriction between SEQ ID NOs:3 and 5 is withdrawn, although these sequences will not be examined.

The restriction requirement is between Groups I and II deemed proper and is therefore made FINAL. Claims 12-18 and 20-21 are withdrawn from consideration as being drawn to non-elected inventions.

2. The drawings filed 20 February 2004 are objected to because it is very difficult to make out the letters in the darkened boxes and because of the strange quality of the letters in the Figure. Corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. See 37 CFR 1.85(a) and MPEP 608.02(b).

Claim Objections

3. Claim 11 is objected to because it recites an improper article before "plant".

4. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The recitation of "A" before "isolated" encompasses nucleic acids that comprise the full-length sequence of the nucleic acid of claim 1 or any portion of the nucleic acid of claim 1. Thus, claim 2 is broader than parent claim 1, and fails to properly limit it.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-11, 19 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding SEQ ID NO:3 or 5, host cells, plants, plant cells and seeds comprising them, and method of using them to make SEQ ID NO:3 or 5, does not reasonably provide enablement for nucleic acids encoding pesticidal protein with 95% identity to SEQ ID NO:3 or 5, nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4, or a complement of those nucleic acids, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 95% identity to SEQ ID NO:3 or 5 and a pesticidal protein encoded by a nucleic acid with 95% identity to SEQ ID NO:1, 2 or 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to nucleic acids encoding a pesticidal protein with 95% identity to SEQ ID NO:3 or 5, nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4, or a complement of those nucleic acids, host cells, plants, plant cells and seeds comprising them, and method of using them to make a pesticidal protein with 95% identity to SEQ ID NO:3 or 5 and a pesticidal protein encoded by a nucleic acid with 95% identity to SEQ ID NO:1, 2 or 4.

The instant specification, however, only discusses sequencing of DNAs from non-publically available bacterial strain ATX13026 (examples 1-4), identification of a nucleic acid, SEQ ID NO:1, that encodes a protein, SEQ ID NO:3, with 66% identity to the delta endotoxin cry40Aa, and an alternate start site variant, SEQ ID NO:4, which encodes SEQ ID NO:5 (examples 5-6), identification of an open reading frame, SEQ ID No:7, encoded by SEQ ID NO:6, downstream of SEQ ID NO:1 with identity to down tream opern reading frames of other cry proteins (example 7); assay of the protein for pesticidal activity against *Trichoplusa ni* (cabbage looper) and *Tenebrio molitor* (yellow mealworm) (examples 7-11), and prophetic guidance for expression in plants (examples 12-14).

The instant specification fails to provide guidance for how to make nucleic acids encoding pesticidal protein with 95% identity to SEQ ID NO:3 or 5 and nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:3 or 5 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein. The specification also fails to provide

guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional protein.

Making substitutions in a protein does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding proteins with 95% identity to SEQ ID NO:3 or 5 or nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4. Making all possible single amino acid substitutions in an 693 amino acid long protein like that encoded by SEQ ID NO:1 or 2 would require making and analyzing 19^{693} nucleic acids; these proteins would have 99.8%% identity to SEQ ID NO:3 or 5. Nucleic acids encoding proteins with 95% identity to SEQ ID NO:3 or 5 would encode proteins with 34 amino acid substitutions. Making all possible single nucleotide substitutions in an 5980 nucleic acid like that of SEQ ID NO:1 would require making and analyzing 4^{5980} nucleic acids and making all possible single nucleotide substitutions in an 2082 nucleic acid like that of SEQ ID NO:2 would require making and analyzing 4^{2208} nucleic acids. Nucleic acids with 95%

identity to SEQ ID NO:1 encompass those that encode proteins with 299 amino acid substitutions; these proteins would have 56% identity to SEQ ID NO:3 or 5. Making all these nucleic acids without guidance as to which amino acid and nucleotide substitutions may be made means that many more than 19^{693} or 4^{5980} nucleic acids would need to be made and analyzed. Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins with up to 299 amino acid substitutions that also have pesticidal activity would require undue experimentation.

Making amino acid substitutions in *cry* proteins is unpredictable. Each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1). Even a single amino acid substitution in a *cry* protein may alter its insecticidal specificity, and toxicity must be determined empirically (Tounsi et al, 2003, J. Appl. Microbiol. 95:23-28; see pg 27, column 2, paragraph 2). For example, a conservative substitution of a lysine for an arginine in a cry11A protein eliminated toxicity to *Aedes aegyptii* (Angsuthanasombat et al, 2001, J. Biochem. Mol. Biol. 34:402-407, paragraph spanning the columns on pg 405).

AXMI-008 has the most similarity to a *cry* protein with toxicity to the dipteran mosquito (cry40Aa; see Ibarra et al, 2003, Appl. Environ. Microbiol. 69:5269-5274; abstract and Table 2). Its toxicity to Lepidopterans *T. ni* and the Coleopteran *T. molitor* suggests that AXMI-008 is a new class of *cry* toxin. Thus, given the novelty of AXMI-008 and the unpredictability making in amino acid substitutions in *cry* proteins, proteins with up to 299 amino acid substitutions

relative to SEQ ID NO:3 or 5 would likely have a very different insect toxicity than AXMI-008, if such toxins could even be made. The specification does not teach the insect toxicity of such proteins. Therefore, one would not know how to use nucleic acids encoding proteins with up to 299 amino acid substitutions relative to SEQ ID NO:3 or 5.

The specification fails to teach how to use a complement of nucleic acids encoding pesticidal protein with 95% identity to SEQ ID NO:3 or 5 or nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4. Complements of DNA molecules are generally used in antisense suppression. Transforming strain ATX13026 with the complement of a nucleic acid encoding a pesticidal protein with 95% identity to SEQ ID NO:3 or 5 or a nucleic acid with 95% identity to SEQ ID NO:1, 2 or 4 could potentially produce a bacterial strain that does not express the pesticidal protein, but the specification does not teach how to use such a bacterial cell. Transforming the cell of any other organism or transforming a plant with the complement of a nucleic acid encoding a pesticidal protein with 95% identity to SEQ ID NO:3 or 5 or a nucleic acid with 95% identity to SEQ ID NO:1, 2 or 4, could not suppress the expression of an endogenous protein, as such an endogenous protein would not be present in the cell. The specification does not teach how to use such a cell or plant.

As the specification does not describe the transformation of any plant with a pesticidal protein with 95% identity to SEQ ID NO:3 or 5, nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4, or a complement of those nucleic acids, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with insect resistance, if such plants are even obtainable.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

7. Claims 1-11, 19 and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A full review of the specification indicates that nucleic acids encoding a pesticidal protein with 95% identity to SEQ ID NO:3 or 5 and nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4, wherein the nucleic acid encodes a pesticidal protein are essential to the operation of the claimed invention. As nucleic acids encoding proteins with 95% identity to SEQ ID NO:3 or 5 would encode proteins with 35 amino acid substitutions and nucleic acids with 95% identity to SEQ ID NO:1 encompass those that encode proteins with 299 amino acid substitutions relative to SEQ ID NO:3 or 5, the claims are drawn to a broad genus of nucleic acids. The level of skill and knowledge in the art at the time of filing was such that no other proteins within the scope of the claims were known

The specification describes no relevant characteristics or motifs for the claimed nucleic acids other than identity to SEQ ID NO:1, 2 or 4. At the time of filing it was known that each *cry* protein only has activity against one or few insect species (de Maagd et al, 1999, Appl. Environ. Microbiol. 65:4369-4374, see pg 4369, column 1, paragraph 1) and that even a single amino acid substitution in a *cry* protein may alter its insecticidal specificity (Tounsi et al, 2003,

J. Appl. Microbiol. 95:23-28; see pg 27, column 2, paragraph 2), but the relationship between structure and pesticidal function was not known. Furthermore, the specification does not describe the structure required for the recited function, nor does it describe the structural features that distinguish pesticidal protein-encoding nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4 from other nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4 or pesticidal proteins with 95% identity to SEQ ID NO:3 or 5 from other proteins with 95% identity to SEQ ID NO:3 or 5.

The only species reduced to practice in the specification is SEQ ID NO:1, 2 or 4, which encodes SEQ ID NO:3 or 5. Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, SEQ ID NO:1, 2 or 4 alone is insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described nucleic acids encoding a pesticidal protein with 95% identity to SEQ ID NO:3 or 5 and nucleic acids with 95% identity to SEQ ID NO:1, 2 or 4, wherein the nucleic acid encodes a pesticidal protein, within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3, 11 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

The phrase "increased GC content" in claim 3 is a relative phrase that renders the claim indefinite. The phrase "increased GC content" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what the GC content is increased relative to.

In claim 11, it is not clear if the seed is transgenic because it comprises the vector or if it transgenic because it was transformed with some other nucleic acid.

In claim 19 it is unclear of the nucleic acid molecule recited in line 2 is the same one in the vector or if it is a different nucleic acid molecule; the recitation of "a" before nucleotide in line 13 suggests the latter.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Barton et al (US Patent 6,833,449, filed August 1989).

Barton et al teach tobacco plants transformed with a nucleic acid encoding a CryI protein (column 10, line 11, to column 11, line 39). It is noted that in the instant claims, the recitation of "a" before "nucleotide sequence of SEQ ID NO:1, 2 or 4" in parts (a) and (b) and "an" before "amino acid sequence of SEQ ID NO:3 or 5" in part (c) encompasses nucleic acids that comprise the full-length sequence of SEQ ID NO:1, 2 or 4, any portion of SEQ ID NO:1, 2 or 4, or that encode the full-length of SEQ ID NO:3 or 5 or any portion of SEQ ID NO:3 or 5. The nucleic acid taught by Barton et al comprises any portion of SEQ ID NO:1, 2 or 4 and encodes any portion of SEQ ID NO:3 or 5.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Anne Kubelik, Ph.D.
February 8, 2006